(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 604 022 A1**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: **93309386.6**

(22) Date of filing: **24.11.93**

(51) Int. Cl.⁵: **A61F 2/06**, A61L 31/00

(30) Priority: **22.12.92 US 995579**

(43) Date of publication of application:
29.06.94 Bulletin 94/26

(84) Designated Contracting States:
BE CH DE FR GB IT LI NL

(71) Applicant: **ADVANCED CARDIOVASCULAR SYSTEMS, INC.**
3200 Lakeside Drive
Santa Clara California 95052(US)

(72) Inventor: **Eury, Robert P.**
10387 B Lockwood Drive
Cupertino, California 95014(US)

(74) Representative: **Baverstock, Michael George Douglas et al**
BOULT, WADE & TENNANT
27 Furnival Street
London, EC4A 1PQ (GB)

(54) **Multilayered biodegradable stent and method for its manufacture.**

(57) A stent (12) of multilayered luminated construction wherein one layer (18) addresses the structural requirements of the stent and additional layers (20,22) release drugs at predictable rates. Both the structural layer (18) as well as the drug releasing layers (20,22) are eventually completely resorbed by the body.

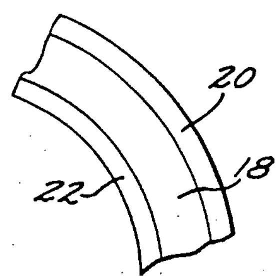

FIG. 2

EP 0 604 022 A1

The present invention relates to expandable intraluminal vascular grafts, generally referred to as stents. More particularly, the invention pertains to stents that are biodegradable and capable of releasing therapeutic drugs.

Stents are implanted within lumens of vessels of the body in order to maintain the patency of such vessels. A variety of delivery systems have been devised that facilitate the placement and deployment of stents. The stent initially is manipulated while in its contracted state, wherein its reduced diameter more readily allows it to be introduced into the lumen and maneuvered into place. Once in place, it is enlarged to a diameter either greater than or equal to the diameter of the lumen so as to allow the free flow of fluids therethrough.

A system especially adapted for coronary applications employs a stent design that incorporates a combination of interacting elements which serve to automatically lock the stent into its enlarged configuration upon expansion. The stent is moved into position along a guidewire that previously has been placed in the lumen where the stent is to be deployed. Inflation of a balloon about which the stent rests causes the stent to expand and lock. Subsequent deflation of the balloon and withdrawal of the catheter and guidewire leaves the stent in place. Elements extending from the surface of the stent engage the vessel walls to positively maintain the stent in position within the lumen.

Stents heretofore typically have been formed of non-toxic, substantially biocompatible metals such as stainless steel, tantalum, or gold. However, it has been determined that typically within about seven to twenty-one days the endothelial layer of the artery or vessel grows into and throughout the walls of the stent, at which point the utility of the stent substantially is diminished and the continued presence of the stent in the lumen may cause any of a variety of problems or complications. Therefore, it has been proposed to form stents of biodegradable or bioabsorbable materials that are completely resorbed by the body within a period of time.

Continued pharmacological treatment of the vessel or condition that made the implantation of the stent necessary often is required or desirable. Such treatment typically is most effective when administered locally and, as a result, it has been suggested to rely on the stent for the delivery of drugs to provide this treatment. Materials are known that are capable of absorbing certain drugs and subsequently releasing the drugs at a substantially predictable rate for a proscribable period of time under particular environmental conditions. By forming the stent of such drug-impregnated material or by otherwise associating such material with the stent, the stent can achieve the dual purpose of maintaining patency and of dispensing drugs.

The prior art has been unable to provide a stent that is completely absorbed by the body after deployment, possesses the physical properties necessary to facilitate its implantation, performs a primary function of maintaining the patency of the vessel for a period of time, and gradually releases a drug prior to its resorption. Previous attempts to impart the necessary physical properties to drug-releasing materials or attempts to impart such properties to those materials without compromising the drug-releasing properties or the efficacy of the drugs absorbed have been unsuccessful.

The present invention provides a stent that is both completely resorbable by the body and capable of delivering certain drugs. Moreover, the stent possesses all the physical properties necessary for it to perform its structural function as well as to facilitate its implantation. This is achieved by employing a multilayered, laminated construction. A first bioabsorbable layer is selected for its physical properties. One or more additional resorbable layers are selected for the ability of the layer or layers to retain various drugs and then gradually release the drugs upon exposure to the particular environment to which the stent is exposed to upon implantation.

The laminated construction allows the combination in a single stent of a plurality of different drug containing materials. By appropriate configuration of the layers, drugs can be either delivered simultaneously with deployment of the stent or released in a predetermined and controlled sequence. Moreover, different parts of the anatomy can be targeted for treatment using different drugs. That is, a drug-containing layer which is associated only with the exterior surface of the stent would cause that drug to be released directly into the vessel wall while a drug-containing layer associated only with the interior surface of the stent would cause the drug to be released into, and to free flow within, the lumen.

The laminated construction of the stent allows the structural layer to be fabricated before it is laminated. Therefore, any layer can be subjected to rigorous conditioning during its processing and treatment that might be advantageous in order to impart sufficient strength to the layer or layers. In the case of prior art stents, this rigorous conditioning might have the effect of deteriorating or causing a degradation in the effect of any drug or drug-releasing materials. The present invention provides for the drug-impregnated materials to be combined with the structural layer only after the fabrication of the structured layer is complete.

The material selected for the structural layer of the stent of the present invention must be reabsorbable while providing the necessary physical char-

acteristics. These requirements can be satisfied by using polymers such as poly-L-lactic acid or polyglycolic acid that have been extruded and oriented to obtain maximum tensile strength and optimal flexural properties.

The drug-releasing layers are selected based on the properties of the materials used to retain sufficient quantities of particular drugs, to release those drugs at a constant or at least predictable rate when exposed to the environment encountered upon implantation, and to eventually become completely absorbed by the body. Polymers capable of such functions include poly-DL-lactic acid or polycaprolactone. Such polymers are first intermixed with the drug or drugs to be delivered and then are either extruded or solvent cast. The drug-containing layer or layers and the structural layer subsequently are laminated to one another using heat or solvents.

The present invention advantageously is applied to stents implantable in a coronary artery after an angioplasty procedure has been performed wherein the exterior surface of the stent releases a drug into the vessel wall that tends to discourage restenosis and also discourages coagulation of the fluid passing through the lumen. Alternatively, a stent according to the present invention may be utilized to treat prostate cancer. In this application, a chemotherapeutic drug is released directly into the urethra via the implanted stent.

These and other features and advantages of the present invention will become apparent from the following detailed description of the preferred embodiments which, taken in conjunction with the accompanying drawings, illustrates by way of example the principles of the invention.

In the drawings:

Figure 1 is a perspective view of a stent of the present invention; and

Figure 2 is an enlarged cross sectional view showing the laminated construction of the stent of Figure 1.

The Figures illustrate a preferred embodiment of the present invention. Generally, Figure 1 illustrates stent 12 prior to implantation. The stent is formed as a furled cylinder of sufficiently small outer diameter so as to be transportable through the lumen in which it is to be deployed and of sufficiently large internal diameter to receive a balloon catheter therein. The tabs 14 extending from the outer surface of the catheter are sized to engage apertures 16 after the balloon has been inflated. The process of inflating the balloon causes the cylinder to unfurl and thereby expand. Once elements 14 and 16 have engaged, the stent effectively is locked into its expanded state and cannot recontract.

Figure 2 is an enlarged crosssectional view of the stent 12 according to the present invention. The stent comprises a laminated structure comprising multiple layers. The particular embodiment illustrated has three layers, layers 18, 20, and 22. Central, relatively thick layer 18 comprises the structural component of the stent which imparts the necessary physical characteristics to make the stent capable of maintaining the patency of a lumen. This central layer also imparts the desired flexural characteristics to the stent to allow it to be positioned as well as to be expanded once positioned. Thinner layers on either side of structural layer 18 deliver pharmacological agents. Materials that form the thinner layers are selected for the ability of the materials to absorb drugs and subsequently release the drugs at predictable rates once the stent is subjected to the environment encountered upon implantation. In the embodiment illustrated, the layers are disposed such that each is adjacent a surface of central structural layer 18. These layers may contain the same type of drug or different drugs. Alternatively, only one drug-releasing layer might be laminated to one surface of the stent. In still another aspect, additional drug-releasing layers can be built up on top of one another to allow sequential release of various medicaments.

The material employed for the structural layer is selected based on the ability of the material to impart the necessary physical properties to the stent as well for its capacity to be completely reabsorbed by the body. "Resorbable" is meant to encompass all those materials that are either biodegradable, bioerodable, or bioabsorbable and includes materials that break down over time and are gradually absorbed or those that are eliminated by the body regardless of whether the degradation mainly is due to hydrolysis or is mediated by metabolic processes. As previously mentioned, the strength of such material must be such that once the stent is in its expanded and locked form, it is capable of maintaining the patency of the vessel into which it is implanted. Additionally, the physical characteristics of the material of the structural layer must be such as to provide flexibility sufficient to allow it to be expanded by, for example, the inflation of a balloon contained therein. Furthermore, a degree of longitudinal flexibility is desirable in order to facilitate transportation of the stent through a potentially tortuous path through the lumen to its intended implantation site.

Materials with the capacity to provide both the structural integrity and resorbability required being resorbable typically are polymeric in nature. Polymers such as poly-L-lactic acid or polyglycolic acid which have been extruded and oriented by known methods to obtain maximum tensile strength as well as optimal flexural properties are well-suited

for such application. Polyorthoesters or polyanhydrides also could be used. In the present invention, the laminated construction of the stent allows the structural layer to be processed and treated to enhance its physical properties without concern for the effect such potentially rigorous conditions would have on drug and drug-containing materials.

The materials used for drug-releasing layers 20 and 22 are selected for the ability to be absorbed and the ability to retain various drugs and subsequently release the medicaments at a predictable rate upon implantation of the stent. Materials found to be especially advantageous for such purposes include polymers such as poly-DL-lactic acid and polycaprolactone. These polymers can be intermixed with the drug or drugs to be released and subsequently extruded or solvent cast by well-known methods.

After the central structural layer and any drug-releasing layers have been fabricated, the layers are laminated to one another using heat or solvents. For example, a layer of poly-L-lactic acid and a poly-DL-lactic acid are combinable by configuring the two layers in intimate contact and subjecting the layers to a temperature of about 55 °C. The completed laminate subsequently is stamped or laser-cut to the appropriate dimensions. The elements and features necessary to initially maintain the stent in a furled state and subsequently allow it to be locked into its expanded state are formed by similarly well known methods. A final furling or shaping operation renders the stent substantially ready for use.

The ultimate purpose of the stent dictates the dimensions of the stent, the strength requirements and physical characteristics of the stent, and the particular drugs and drug delivery rates selected. For example, when the goal is to maintain the patency of a coronary artery, a stent according to the present invention wherein the innermost layer exposed to the lumen is configured to release a drug that reduces the likelihood of thrombosis. Heparin or prostacyclin are among the drugs appropriate for this purpose. In such an application, outer layer 20 could advantageously release drugs that address restenosis. Drugs that have been found to be effective for this purpose include angiopeptin, methotrexate, and heparin.

While a particular form of the invention has been illustrated and described, it also will be apparent to those skilled in the art that various modifications can be made without departing from the spirit and scope of the invention. Any of a variety of stent designs and applications can benefit from the present invention. Accordingly, it is not intended that the invention be limited except by the appended claims.

Claims

1. An expandable intraluminal stent for implantation in a vessel, comprising:
   a first layer formed of resorbable material selected to impart structural rigidity to said stent; and
   a second layer of a resorbable material, joined to said first layer and selected to release a therapeutic drug at a selected rate therefrom, whereby upon implantation, said stent initially provides a desired degree of structural support to said vessel, releases said drug at the selected rate and eventually is completely resorbed.

2. A stent as claimed in claim 1, wherein said first layer is further selected to impart additional desired physical characteristics to said stent.

3. A stent as claimed in claim 1, wherein said first layer comprises poly-L-lactic acid, or polyglycolic acid.

4. A stent as claimed in any one of claims 1 to 3, wherein said second layer comprises poly-DL-lactic acid or polycaprolactone.

5. A stent as claimed in any one of the preceding claims wherein said stent is implantable in a lumen upstream from a cancerous growth and said second layer is selected to release a chemotherapeutic drug.

6. A stent as claimed in any one of the preceding claims wherein said second layer is selected to release heparin.

7. A stent as claimed in any one of the preceding claims wherein a third layer of resorbable material is joined to said first layer and selected to release a therapeutic drug at a selected rate therefrom, whereby upon implantation, said stent initially provides a desired degree of structural support to said vessel, releases said drugs at the selected rates and eventually is completely resorbed.

8. A stent as claimed in claim 7, wherein the drugs released by said first and second layer are identical.

9. A stent as claimed in claim 7, wherein the drugs released by said first and second layer are different.

10. A stent as claimed in claim 9, wherein said stent is implantable within a coronary artery,

said second layer is joined to the outer side of said stent's first layer and releases a drug that addresses restenosis and said third layer is joined to the inner side of said stent's first layer and releases a drug that addresses thrombosis.

11. A stent as claimed in claim 7, wherein said second layer is selected to release angiopeptin and said third layer is selected to release heparin.

12. A method of fabricating a biodegradable, drug releasing stent for implantation within a lumen, comprising the steps of:

forming a first layer of biodegradable material having physical properties necessary to enable a stent to perform its structural function within said lumen;

forming a second layer of biodegradable material which releases a selected drug upon exposure to an environment such as is encountered within said lumen; and

joining said second layer to said first layer to provide a laminated structure that is biodegradable, drug releasing and has the physical properties necessary for said stent to perform its structural function within said lumen.

13. A method as claimed in claim 12, further comprising the steps of:

forming a third layer of biodegradable material which releases a selected drug upon exposure to an environment such as is encountered within said lumen; and

joining said third layer to said first layer.

14. A method as claimed in claim 12 or claim 13, wherein said first layer is formed by extrusion and orientation of a polymeric material.

15. A method as claimed in claim 14, wherein said polymeric material comprises poly-L-lactic acid or polyglycolic acid.

16. A method as claimed in any one of claims 12 to 15, wherein said second layer comprises a mixture of said drug and a polymeric material.

17. A method as claimed in claim 16, wherein said polymeric material comprises poly-DL-lactic acid or a polycaprolactone.

18. A method as claimed in any one of claims 12 to 17, wherein said second layer is joined to said first layer with the application of heat or with the use of solvents.

19. A method as claimed in any one of claims 13 to 17, wherein said second and third layers are joined to said first layer with the application of heat or with the use of solvents.

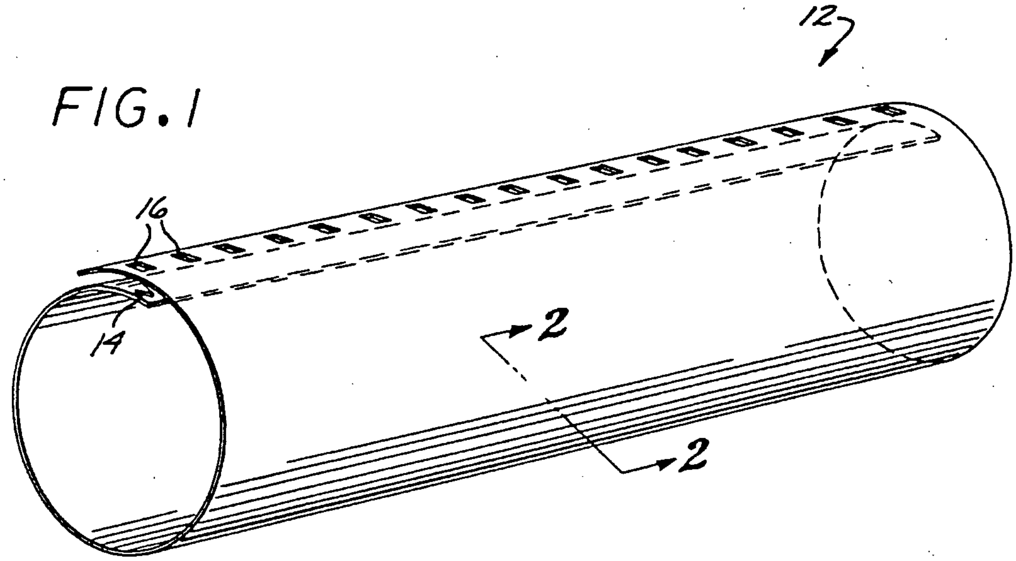

FIG. 1

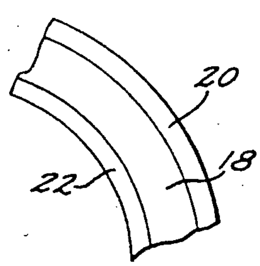

FIG. 2

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 30 9386

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
X Y	WO-A-90 01969 (M-J. SLEPIAN) * page 10, line 27 - page 14, line 5; figures 1-8 * * page 24, line 26 - line 31 * ---	1-9,12, 13,16-19 10,11, 14,15	A61F2/06 A61L31/00
Y A	WO-A-91 17744 (G.R. JERNBERG) * page 6, line 32 - page 7, line 21 * * page 9, line 3 - line 16 * * page 10, line 2 - line 29; claims 9,18,22,35,36; figures 4A-4D * ---	10,11 1-4,6-9	
Y A	WO-A-90 04982 (BIOCON) * abstract * * page 16, line 26 - page 17, line 6; table 1 * ---	14,15 1-5	
X	WO-A-91 17789 (R.S. STACK ET AL.) * page 17, line 32 - line 36 * * page 21, line 18 - page 22, line 11 * * page 23, line 12 - line 16 * ---	1-3,6, 12,16	**TECHNICAL FIELDS SEARCHED (Int.Cl.5)** A61F A61L A61M
A	EP-A-0 364 787 (EXPANDABLE GRAFTS PARTNERSHIP) * column 12, line 48 - line 57; figures 5,6 * ---	1,4,12	
A	US-A-5 100 429 (E.L. SINOVSKY ET AL.) * column 8, line 43 - line 52; figures 6,7 * * column 9, line 37 - line 66 * --- -/--	1-3, 12-19	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	28 February 1994	Wolf, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 30 9386

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
A	WO-A-92 10218 (W.L. GORE & ASSOCIATES) * page 7, line 8 - line 34; figures 2,4,12 * * page 9, line 19 - line 27 * * page 12, line 24 - line 31 * ---	1-10,12, 13,15, 16,18,19	
A	WO-A-90 06094 (BRIGHAM AND WOMEN'S HOSPITAL) * page 9, line 22 - line 26 * * page 14, line 15 - page 15, line 25 * ---	1,2, 5-13,16, 18,19	
A	EP-A-0 493 788 (MUDR. MILAN KRAJICEK CSC.) * column 2, line 12 - column 3, line 9; figure * ---	7-11	
A	WO-A-89 03232 (BUKH MEDITEC) * abstract; claims 4,7,16 * ---	1-5, 12-16, 18,19	TECHNICAL FIELDS SEARCHED (Int.Cl.5)
P,X	WO-A-93 06792 (SCIMED LIFE SYSTEMS) * abstract * * page 12, line 5 - page 13, line 2 * * page 18, line 24 - line 30 * * page 19, line 24 - page 21, line 17 * * page 22, line 10 - page 23, line 2 * -----	1-19	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	28 February 1994	Wolf, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 623 354 A1**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: **94302807.6**

(51) Int. Cl.[5]: **A61L 31/00,** A61F 2/06

(22) Date of filing: **20.04.94**

(30) Priority: **26.04.93 US 52878**

(43) Date of publication of application: **09.11.94 Bulletin 94/45**

(84) Designated Contracting States: **DE FR NL**

(71) Applicant: **MEDTRONIC, INC.**
7000 Central Avenue N.E.
Minneapolis, Minnesota 55432-3576 (US)

(72) Inventor: **Berg, Eric P.**
18710 Fourth Place North
Plymouth, Minnesota 55447 (US)
Inventor: **Tuch, Ronald J.**
12330 51st Avenue North
Plymouth, Minnesota 55442 (US)
Inventor: **Dror, Michael**
6227 Westridge Boulevard
Edina, Minnesota 55436 (US)
Inventor: **Wolff, Rodney G.**
2316 Lafayette Road
Minnetonka Beach, Minnesota 55361 (US)

(74) Representative: **Cockbain, Julian, Dr.**
Frank B. Dehn & Co.
Imperial House
15-19, Kingsway
London WC2B 6UZ (GB)

(54) **Intravascular stents.**

(57) The invention provides a method for making an intravascular stent by applying to the body of a stent a solution which comprises a solvent, a polymer dissolved in the solvent and a therapeutic substance dispersed in the solvent and then evaporating the solvent. The inclusion of a polymer in intimate contact with a drug on the stent allows the drug to be retained on the stent during expansion of the stent and also controls the administration of drug following implantation. The adhesion of the coating and the rate at which the drug is delivered can be controlled by the selection of an appropriate bioabsorbable or biostable polymer and the ratio of drug to polymer in the solution. By this method, drugs such as dexamethasone can be applied to a stent, retained on a stent during expansion of the stent and elute at a controlled rate.

EP 0 623 354 A1

This invention relates to intravascular stents for treatment of injuries to blood vessels and particularly to stents having a framework onto which a therapeutic substance or drug is applied.

Although angioplasty procedures have increased greatly in popularity for treatment of occluded arteries, the problem of restenosis following the angioplasty treatment remains a significant problem. Restenosis is the closure of a peripheral or coronary artery following trauma to the artery caused by efforts to open an occluded portion of the artery by angioplasty, such as, for example, by balloon dilation, atherectomy or laser ablation treatment of the artery. For these angioplasty procedures, restenosis occurs at a rate of about 30-60% depending upon the vessel location, lesion length and a number of other variables.

One aspect of restenosis may be simply mechanical; e.g. caused by the elastic rebound of the arterial wall and/or by dissections in the vessel wall caused by the angioplasty procedure. These mechanical problems have been successfully addressed by the use of stents to tack-up dissections and prevent elastic rebound of the vessel, thereby reducing the level of restenosis for many patients. The stent is typically inserted by catheter into a vascular lumen and expanded into contact with the diseased portion of the arterial wall, thereby providing internal support for the lumen. Examples of stents which have been successfully applied over a PTCA balloon and radially expanded at the same time as the balloon expansion of an affected artery include the stents disclosed in US-A-4733665 (Palmaz), US-A-4800882 (Gianturco) and US-A-4886062 (Wiktor) which are incorporated herein by reference in their entirety.

Another aspect of restenosis is believed to be a natural healing reaction to the injury of the arterial wall that is caused by angioplasty procedures. The final result of the complex steps of the healing process is intimal hyperplasia, the migration and proliferation of medial smooth muscle cells, until the artery is again occluded.

To address both aspects of the restenosis problem, it has been proposed to provide stents which are seeded with endothelial cells (see Dichek,D.A. et al. "Seeding of Intravascular Stents With Genetically Engineered Endothelial Cells", Circulation 80: 1347-1353 (1989)). In that experiment, sheep endothelial cells that had undergone retrovirus-mediated gene transfer for either bacterial beta-galactosidase or human tissue-type plasminogen activator were seeded onto stainless steel stents and grown until the stents were covered. The cells were therefore able to be delivered to the vascular wall where they could provide therapeutic proteins. Other methods of providing therapeutic substances to the vascular wall include simple heparin-coated metallic stents, whereby a heparin coating is ionically or covalently bonded to the stent. Still other methods of providing therapeutic substances to the vascular wall by means of stents have also been proposed such as in US-A-5102417 (Palmaz), WO-91/12779 "Intraluminal Drug Eluting Prosthesis" and WO-90/13332 "Stent With Sustained Drug Delivery". In the latter two, it is suggested that antiplatelet agents, anticoagulant agents, antimicrobial agents, antimetabolic agents and other drugs could be supplied in stents to reduce the incidence of restenosis.

Metal stents such as those disclosed in US-A-4733665 (Palmaz), US-A-4800882 (Gianturco) and US-A-4886062 (Wiktor) could be suitable for drug delivery in that they are capable of maintaining intimate contact between a substance applied to the outer surface of the stent and the tissues of the vessel to be treated. However, there are significant problems to be overcome in order to secure a therapeutically significant amount of a substance onto the metal of the stent; to keep it on the stent during expansion of the stent into contact with the blood vessel wall; and also controlling the rate of drug delivery from the drug on the stent to the vessel wall.

There thus remains a need for means for providing a stent having a therapeutically significant amount of a drug applied thereto.

We have discovered a method for making an intravascular stent which meets this need.

Viewed from one aspect therefore the invention provides a method for making an intravascular stent comprising the steps of:

(a) providing a generally cylindrical stent body;

(b) applying to the stent body a solution which comprises a solvent, a polymer dissolved in the solvent and a therapeutic substance dispersed in the solvent; and

(c) evaporating said solvent.

Viewed from a further aspect the invention provides the use of a solution containing a dissolved polymer and a dispersed therapeutic substance for the manufacture of a therapeutic agent comprising an intravascular stent having a polymeric drug-eluting surface coating.

Viewed from a still further aspect the invention provides stents made by the method of the invention.

In the method of the invention there is applied to the body of a stent, and in particular to its tissue-contacting surface, a solution which includes a solvent, a polymer dissolved in the solvent and a therapeutic substance (i.e. a drug) dispersed in the solvent, and the solvent thereafter is evaporated to leave a drug-elating polymeric surface on the stent. The inclusion of a polymer in intimate contact with a drug on the stent allows the drug to be retained on the stent in a resilient matrix during expansion of the stent and also slows the administration of drug following implantation. The method of the invention can be used whether the stent has a metallic or

polymeric surface. The method is also an extremely simple one since it can be effected by simply immersing the stent into the solution or by spraying the solution onto the stent. The amount of drug to be included on the stent can be readily controlled by applying multiple thin coats of the solution while allowing it to dry between coats. The overall coating should be generally thin enough so that it will not significantly increase the profile of the stent for intravascular delivery by catheter. It is therefore preferably less than about 0.002 inch (0.05 mm) thick and most preferably less than 0.001 inch (0.025 mm) thick. The adhesion of the coating and the rate at which the drug is delivered can be controlled by the selection of an appropriate bioabsorbable or biostable polymer and by the ratio of drug to polymer in the solution. By this method, drugs such as glucocorticoids (e.g. dexamethasone, betamethasone), heparin, hirudin, tocopherol, angiopeptin, aspirin, ACE inhibitors, growth factors, oligonucleotides, and, more generally, antiplatelet agents, anticoagulant agents, antimitotic agents, antioxidants, antimetabolite agents, and anti-inflammatory agents can be applied to a stent, retained on a stent during expansion of the stent and elute the drug at a controlled rate. The release rate can be further controlled by varying the ratio of drug to polymer in the multiple layers. For example, a higher drug-to-polymer ratio in the outer layers than in the inner layers would result in a higher early dose which would decrease over time.

In operation, the stent made according to the present invention can deliver drugs to a body lumen by introducing the stent transluminally into a selected portion of the body lumen and radially expanding the stent into contact with the body lumen. The transluminal delivery can be accomplished by a catheter designed for the delivery of stents and the radial expansion can be accomplished by balloon expansion of the stent, by self-expansion of the stent, or a combination of self-expansion and balloon expansion.

Thus the present invention provides a stent which may be delivered and expanded in a selected blood vessel without losing a therapeutically significant amount of a drug applied thereto. It also provides a drug-containing stent which allows for a sustained release of the drug to vascular tissue.

The underlying structure of the stent used according to the invention can be virtually any stent design, for example of the self-expanding type or of the balloon-expandable type, and of metal or polymeric material. Thus metal stent designs such as those disclosed in US-A-4733665 (Palmaz), US-A-4800882 (Gianturco) and US-A-4886062 (Wiktor) could be used in the present invention. The stent could be made of virtually any bio-compatible material having physical properties suitable for the design. For example, tantalum and stainless steel have been proven suitable for many such designs and could be used in the present invention. Also, stents made with biostable or bioabsorbable polymers such as poly(ethylene terephthalate), polyacetal, poly(lactic acid), poly(ethylene oxide)/poly(butylene terephthalate) copolymer could be used in the present invention. Although the stent surface should be clean and free from contaminants that may be introduced during manufacturing, the stent surface requires no particular surface treatment in order to retain the coating applied in the present invention. Both the inner and outer surfaces of the stent may be provided with the coating according to the present invention.

In order to provide the coated stent according to the present invention, a solution which includes a solvent, a polymer dissolved in the solvent and a therapeutic substance dispersed in the solvent is first prepared. The solvent, polymer and therapeutic substance should of course be mutually compatible. The solvent should be capable of placing the polymer into solution at the concentration desired. Moreover the solvent and polymer should not chemically alter the therapeutic character of the therapeutic substance. However, the therapeutic substance only needs to be dispersed throughout the solvent so that it may be either in a true solution with the solvent or dispersed in fine particles in the solvent. Examples of some suitable combinations of polymer, solvent and therapeutic substance are set forth in Table 1 below.

TABLE 1

POLYMER	SOLVENT	THERAPEUTIC SUBSTANCE
poly(L-lactic acid)	chloroform	dexamethasone
poly(lactic acid-co-glycolic acid)	acetone	dexamethasone
polyether urethane	N-methyl pyrrolidone	tocopherol (vitamin E)
silicone adhesive	xylene	dexamethasone phosphate
poly(hydroxybutyrate-co-hydroxy-valerate)	dichloromethane	aspirin
fibrin	water (buffered saline)	heparin

The solution is applied to the stent and the solvent is allowed to evaporate, thereby leaving on the stent surface a coating of the polymer and the therapeutic substance. Typically, the solution can be applied to the stent by either spraying the solution onto the stent or immersing the stent in the solution. Whether one chooses application by immersion or application by spraying depends principally on the viscosity and surface tension of the solution, however, it has been found that spraying in a fine spray such as that available from an airbrush will provide a coating with the greatest uniformity and will provide the greatest control over the amount of coating material to be applied to the stent. In either a coating applied by spraying or by immersion, multiple application steps are generally desirable to provide improved coating uniformity and improved control over the amount of therapeutic substance to be applied to the stent.

The polymer chosen should be a polymer that is biocompatible and minimizes irritation to the vessel wall when the stent is implanted. The polymer may be either a biostable or a bioabsorbable polymer depending on the desired rate of release or the desired degree of polymer stability, but a bioabsorbable polymer may be more desirable since, unlike a biostable polymer, it will not be present long after implantation to cause any adverse, chronic local response. Bioabsorbable polymers that could be used include poly(L-lactic acid), polycaprolactone, poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(D,L-lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), copoly(etheresters) (e.g. PEO/PLA), polyalkylene oxalates, polyphosphazenes and biomolecules such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid. Also, biostable polymers with a relatively low chronic tissue response such as polyurethanes, silicones, and polyesters could be used and other polymers could also be used if they can be dissolved and cured or polymerized on the stent such as polyolefins, polyisobutylene and ethylene-alphaolefin copolymers; acrylic polymers and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile, polyvinyl ketones; polyvinyl aromatics, such as polystyrene, polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers; polyamides, such as Nylon 66 and polycaprolactam; alkyd resins; polycarbonates; polyoxymethylenes; polyimides; polyethers; epoxy resins, polyurethanes; rayon; rayon-triacetate; cellulose, cellulose acetate, cellulose butyrate; cellulose acetate butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers; and carboxymethyl cellulose.

The ratio of therapeutic substance to polymer in the solution will depend on the efficacy of the polymer in securing the therapeutic substance onto the stent and the rate at which the coating is to release the therapeutic substance to the tissue of the blood vessel. More polymer may be needed if it has relatively poor efficacy in retaining the therapeutic substance on the stent and more polymer may be needed in order to provide an elution matrix that limits the elution of a very soluble therapeutic substance. A wide ratio of therapeutic substance to polymer could therefore be appropriate and the weight ratio could range from about 10:1 to about 1:100.

The therapeutic substance used in the present invention could be virtually any therapeutic substance which possesses desirable therapeutic characteristics for application to a blood vessel. This can include both solid substances and liquid substances. For example, glucocorticoids (e.g. dexamethasone, betamethasone), heparin, hirudin, tocopherol, angiopeptin, aspirin, ACE inhibitors, growth factors, oligonucleotides, and, more generally, antiplatelet agents, anticoagulant agents, antimitotic agents, antioxidants, antimetabolite agents, and anti-inflammatory agents could be used. Antiplatelet agents can include drugs such as aspirin and dipyridamole. Aspirin is classified as an analgesic, antipyretic, anti-inflammatory and antiplatelet drug. Dipyridimole is a drug similar to aspirin in that it has anti-platelet characteristics. Dipyridimole is also classified as a coronary vasodilator. Anticoagulant agents can include drugs such as heparin, coumadin, protamine, hirudin and tick anticoagulant protein. Antimitotic agents and antimetabolite agents can include drugs such as methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, adriamycin and mutamycin.

Embodiments of the invention will now be described further with reference to the following non-limiting Examples and the accompanying drawings, in which:

Fig. 1 is a plot showing elution profiles for stents according to the present invention with a coating of dexamethasone and poly(L-lactic acid) made according to Example 6; and

Fig. 2 is a plot showing elution profiles for sterilized stents according to the present invention with a coating of dexamethasone and poly(L-lactic acid) made according to Example 7.

In the Examples percentages and ratios are by weight unless otherwise stated.

EXAMPLE 1 (COMPARATIVE)

A 1% solution of dexamethasone in acetone was made, forming a clear solution. The solution was placed

in an airbrush reservoir (Badger #200). Wiktor type tantalum wire stents were sprayed with the solution in short bursts while rotating the stents. The acetone quickly evaporated from the stents, leaving a white residue on the stent wire. The process was continued until all of the stent wires were coated. The drug elution rate for the stent was determined by immersing the stent in phosphate buffered saline solution (pH=7.4). Traces of dexamethasone were observed to remain on the immersed stents for less than 31 hours.

EXAMPLE 2 (COMPARATIVE)

A 2% solution of dexamethasone in acetone was made, forming a solution with suspended particles of dexamethasone. The solution was placed into a tube. Wiktor type tantalum wire stents were dipped rapidly and were allowed to dry. Each stent was dipped into the solution 12-15 times to provide a white surface coating. Two stents were placed on an angioplasty balloon and were inflated on the balloon. Approximately 80% of the dexamethasone coating flaked off of the stents.

EXAMPLE 3

A solution of 1% dexamethasone and 0.5% poly(caprolactone) (Aldrich 18,160-9) in acetone was made. The solution was placed into a tube. Wiktor type tantalum wire stents were dipped rapidly and were allowed to dry. Each stent was dipped into the solution 12-15 times to provide a white surface coating. A stent so coated was expanded on a 3.5mm angioplasty balloon causing a significant amount of the coating to become detached.

EXAMPLE 4

A solution of 1% dexamethasone and 0.5% poly(L-lactic acid) (Medisorb) in acetone was made. The solution was placed into a tube. Wiktor type tantalum wire stents were dipped rapidly and were allowed to dry. Each stent was dipped into the solution 12-15 times to provide a white surface coating. A stent so coated was expanded on a 3.5mm angioplasty balloon causing only a small portion of the coating (less than 25%) to become detached)

EXAMPLE 5

A solution including a 2% dispersion of dexamethasone and a 1% solution of poly(L-lactic acid) (CCA Biochem MW=550,000) in chloroform was made. The solution was placed into an airbrush (Badger). Wiktor type tantalum wire stents were sprayed in short bursts and were allowed to dry. Each stent was sprayed with the solution about 20 times to provide a white surface coating. A stent so coated was expanded on a 3.5mm angioplasty balloon. The coating remained attached to the stent throughout the procedure.

EXAMPLE 6

A solution including a 2% dispersion of dexamethasone and a 1% solution of poly(L-lactic acid) (CCA Biochem MW=550,000) in chloroform was made. The solution was placed into an airbrush (Badger #250-2). Wiktor type tantalum wire stents were suspended from a fixture and sprayed in 24 short bursts (6 bursts from each of the four directions perpendicular to the stent axis) and were allowed to dry. The resulting stents had a coating weight of about 0.0006-0.0015 grams. Three of the stents were tested for long term elution by placing one stent in 3.0 ml of phosphate buffered saline solution (pH=7.4) at ambient temperature without stirring. The amount of dexamethasone eluted was evaluated by measuring absorbance at 244 nm in a UV-VIS spectrophotometer. The results of this test are shown in Figure 1.

EXAMPLE 7

A solution including a 2% dispersion of dexamethasone and a 1% solution of poly(L-lactic acid) (Medisorb 100-L) in chloroform was made along with a control solution of 1% of poly(L-lactic acid) (Medisorb 100-L) in chloroform. The solutions were placed into an airbrush (Badger #250-2). Wiktor type tantalum wire stents were expanded on a 3.0mm balloon, suspended from a fixture and sprayed in 16 short bursts (2-3 bursts of about 1 second followed by several minutes drying time between applications). The resulting dexamethasone-coated stents had an average coating weight of about 0.0012 grams while the polymer-coated stents had an average polymer weight of about 0.0004 grams. The stents were sterilized in ethylene oxide. Three of the sterilized

dexamethasone-coated stents were tested for long term elution by placing one stent in 3.0 ml of phosphate buffered saline solution (pH=7.4) at ambient temperature without stirring. The amount of dexamethasone eluted was evaluated by measuring absorbance at 244 nm in a UV-VIS spectrophotometer. The results of this test are shown in Figure 2. Dexamethasone-coated stents and polymer-coated control stents were implanted in the coronary arteries of 8 pigs (N=12 for each type) according to the method set forth in "Restenosis After Balloon Angioplasty - A Practical Proliferative Model in Porcine Coronary Arteries," by Robert S. Schwartz et al., Circulation 82(6):2190-2200 (1990), and "Restenosis and the Proportional Neointimal Response to Coronary Artery Injury: Results in a Porcine Model" by Robert S. Schwartz et al., J Am Coll Cardiol 19:267-274 (1992) with the result that when compared with the controls, the dexamethasone-coated stents reduced the amount of proliferation associated with the arterial injury.

Claims

1. A method for making an intravascular stent comprising the steps of:
   (a) providing a generally cylindrical stent body;
   (b) applying to the stent body a solution which comprises a solvent, a polymer dissolved in the solvent and a therapeutic substance dispersed in the solvent; and
   (c) evaporating said solvent.

2. A method as claimed in claim 1 wherein said stent body has a metal surface.

3. A method as claimed in claim 1 wherein said stent body has a polymeric surface.

4. A method as claimed in any one of claims 1 to 3 wherein said solution is applied to said body by spraying.

5. A method as claimed in any one of claims 1 to 3 wherein said solution is applied to said body by immersion.

6. A method as claimed in any one of claims 1 to 5 wherein said solution is applied to said body in a plurality of application and drying steps.

7. A method as claimed in claim 6 wherein the concentration ratio of said therapeutic substance to said polymer in said solution is varied between some of said plurality of application steps.

8. A method as claimed in any one of claims 1 to 7 wherein said polymer is a bioabsorbable polymer.

9. A method as claimed in claim 8 wherein said polymer is selected from poly(L-lactic acid), poly(lactide-co-glycolide) and poly(hydroxybutyrate-co-valerate).

10. A method as claimed in any one of claims 1 to 7 wherein said polymer is a biostable polymer.

11. A method as claimed in claim 10 wherein said polymer is selected from silicones, polyurethanes, polyesters, vinyl homopolymers and copolymers, acrylate homopolymers and copolymers, polyethers and cellulosics.

12. A method as claimed in any one of claims 1 to 7 wherein said polymer is selected from poly(L-lactic acid), poly(lactide-co-glycolide), fibrin, silicone, polyurethane, and poly(phosphoester urethane).

13. A method as claimed in any one of claims 1 to 12 wherein the weight ratio of said therapeutic substance to said polymer in said solution is in the range of about 10:1 to 1:100.

14. A method as claimed in any one of claims 1 to 13 wherein said therapeutic substance is selected from glucocorticoids, dexamethasone, dexamethasone sodium phosphate, anticoagulants, heparin, hirudin, tick anticoagulant peptide, angiopeptin, antimitotic agents, and oligonucleotides.

15. A method as claimed in claim 14 wherein said therapeutic substance is dexamethasone.

16. A method as claimed in any one of claims 1, 2, 5 to 9 and 12 to 15 comprising the steps of:
   (a) providing a generally cylindrical metal stent body;
   (b) spraying onto the stent body a solution which comprises a solvent, a bioabsorbable polymer dis-

solved in said solvent and a glucocorticoid dispersed in said solvent; and
(c) evaporating said solvent.

17. The use of a solution containing a dissolved polymer and a dispersed therapeutic substance for the manufacture of a therapeutic agent comprising an intravascular stent having a polymeric drug-eluting surface coating.

18. A stent made by a method as claimed in any one of claims 1 to 16.

19. A stent having a polymeric, dexamethasone-releasing coating.

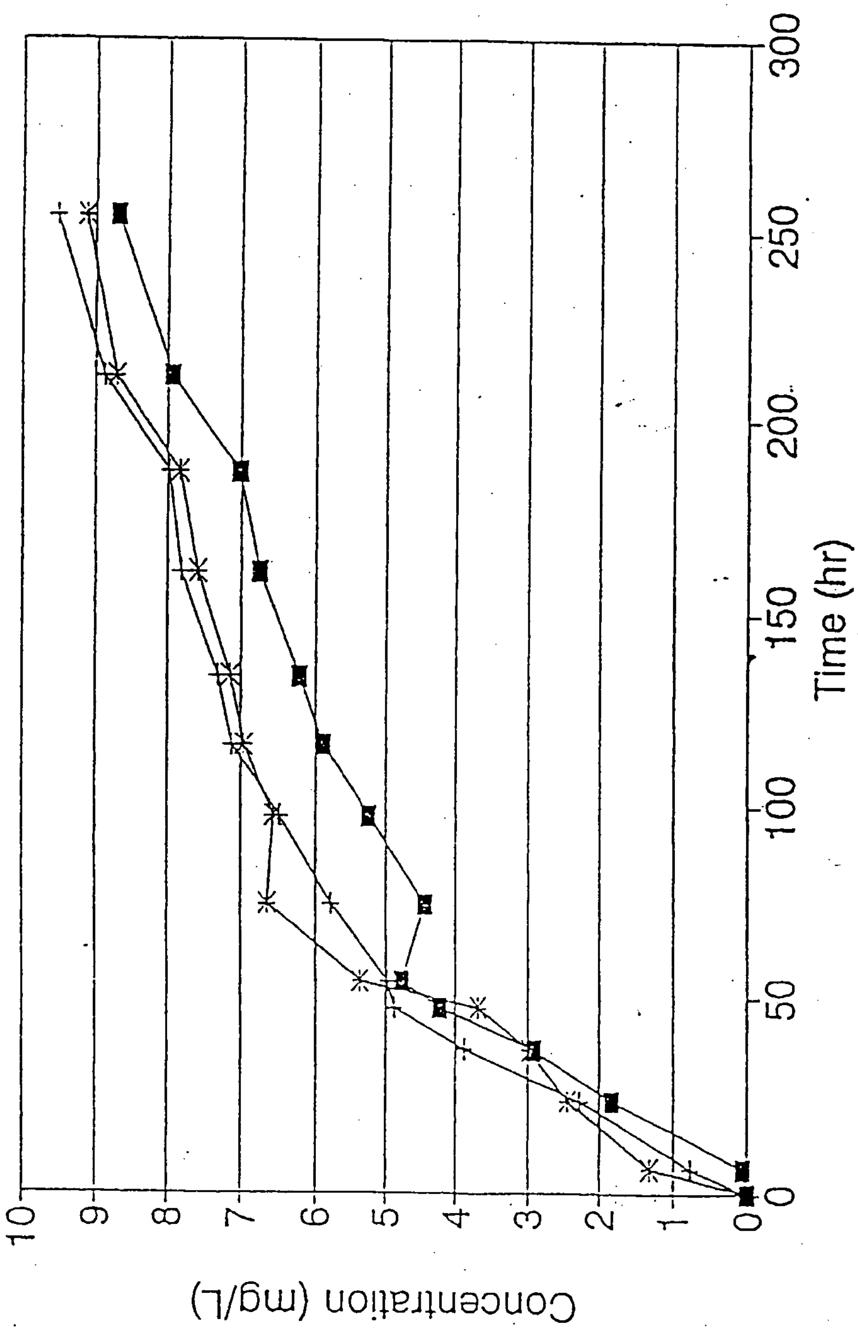
Concentration (mg/L)
Time (hr)
0
1
2
3
4
5
6
7
8
9
10
50
100
150
200
250
300

Fig. 1

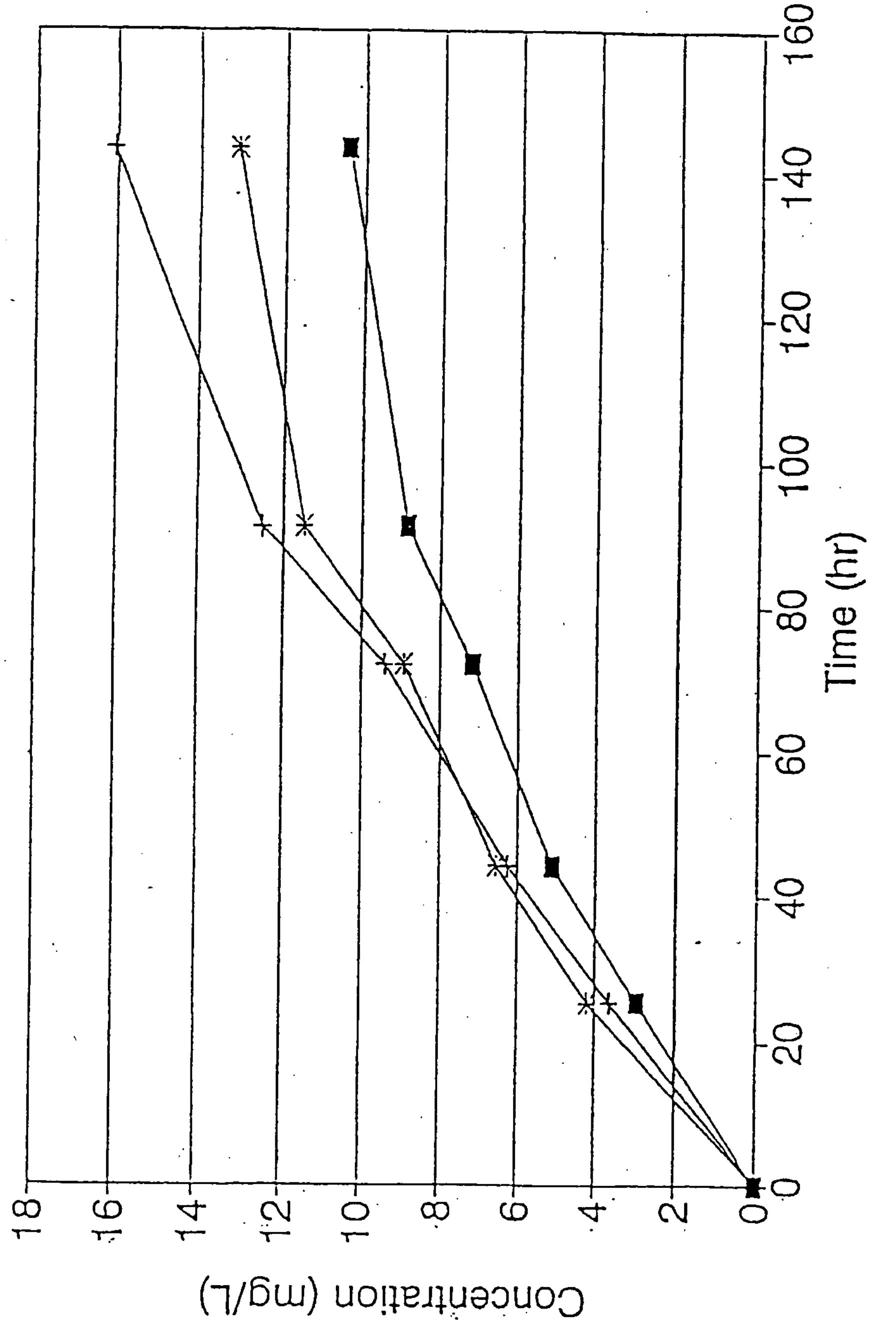
Concentration (mg/L)
0
2
4
6
8
10
12
14
16
18
Time (hr)
0
20
40
60
80
100
120
140
160

Fig. 2

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 30 2807

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
X	WO-A-92 15286 (NOVA PHARMACEUTICAL CORP.) 17 September 1992 * page 9, line 6 - line 17 * * page 10; example 7 *	1-19	A61L31/00 A61F2/06
X	WO-A-91 18940 (NOVA PHARMACEUTICAL CORP.) 12 December 1991 * page 6, line 1 * * page 10, line 18 - line 20 * * page 11, line 1 - line 5 * * page 27, line 20 - line 23; claims *	1-8	
X	WO-A-93 06792 (SCIMED LIFE SYSTEMS, INC.) 15 April 1993 * page 21, line 18 - line 31; claims *	1	
A	WO-A-91 17789 (STACK, RICHARD,S. ET AL.) 28 November 1991 * page 21, line 18 - line 37 * * page 22, line 1 - line 3 * * page 27, line 11 - line 14 *	1-19	**TECHNICAL FIELDS SEARCHED (Int.Cl.5)**
D,A	WO-A-91 12779 (MEDTRONIC, INC.) 5 September 1991 * page 3, line 4 - line 14 * * page 10, line 32 - line 38 * * page 12, line 23 - line 28 * * page 13, line 5 - line 6 * * page 13, line 16 - line 17 *	1	A61L A61F
P,X	EP-A-0 566 245 (MEDTRONIC, INC.) 20 October 1993 * column 6, line 2 - line 17 * * column 8, line 19 - line 21 *	1	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	25 August 1994	ESPINOSA, M

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document